DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
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Date: December 12, 1997

From: Jeffrey N. Siegel, M.D., Safety Reviewer for BLA#97-0736

Subject: Safety review for Zenapax

To: Karen Weiss, M.D., Director, OTRR/DCTDA

Through: Dr. William Schwieterman, M.D., Chief, Immunology and Infectious Diseases Branch/ OTRR/DCTDA

WBS - 12/12/97

CC: Jay Siegel, M.D., Director OTRR

1. Attached is Safety Review for Zenapax

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SIGN-OFF SHEET FOR ZENAPAX SAFETY REVIEW

Jeffrey N. Siegel 12/12/97

Jeffrey N. Siegel, M.D., Medical Officer, DCTDA

12/12/97

Dr. William Schwieterman, M.D., Chief, Immunology and Infectious Diseases Branch/ OTRR/DCTDA

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Summary of data submitted

In support of their application for Zenapax (daclizumab), Hoffmann-LaRoche has submitted safety data from 630 subjects in studies of renal allograft rejection of which 336 received Zenapax (daclizumab) and 247 subjects in studies of graft-versus-host disease and Tac-bearing tumors of which 182 received Zenapax (daclizumab). In the studies of renal allograft rejection and graft-versus-host disease, all subjects were treated with Zenapax (daclizumab) in addition to cyclosporin A and other immunosuppressive drugs while in the studies of patients with Tac-bearing tumors, Zenapax (daclizumab) was given alone.

Adverse events

In the studies of renal transplant rejection, most of the subjects experienced one or more adverse events, but the addition of Zenapax (daclizumab) to two– or three–drug immunosuppressive therapy did not result in an increase in the incidence of adverse events (Zenapax 95% vs placebo 95%) or changes in the types of adverse events reported (table 1). The most common body system affect was gastrointestinal, reported by 67% of the patients in the HAT group and 68% of the patients in the placebo group. Of these, constipation, nausea, diarrhea, vomiting, and abdominal pain were reported most frequently in both treatment groups.

Table 1. Most Frequently Reported Adverse Events (>5% of patients in either group) during the first 3 months post-transplant

Body system disorder	Zenapax (n=336)		Placebo (n=293)	
Adverse event	No. pts	%	No. pts	%
Gastrointestinal system disorder	226	67	199	68
Constipation	117	35	111	38
Nausea	92	27	76	26
Diarrhea	51	15	48	16
Vomiting	50	15	42	14
Abdominal pain	33	9.8	38	13
Pyrosis	28	8.3	28	9.6
Dyspepsia	23	6.8	15	5.1
Abdominal distention	19	5.7	13	4.4
Epigastric pain, not food–related	18	5.4	11	3.8
Metabolic and Nutritional Disorders	151	45	146	50

Edema extremities	94	28	88	30.0
Edema	53	16	54	18
Fluid overload	11	3.3	17	5.8
Metabolic and Nutritional Disorders	151	45	146	50
Edema extremities	94	28	88	30
Edema	53	16	54	18
Fluid overload	11	3.3	17	5.8
Central & Peripheral Nervous System Disorders	155	46	119	41
Tremor	65	19	46	16
Headache	52	16	43	15
Dizziness	17	5.1	13	4.4
Urinary System Disorders	132	39	132	45
Oliguria	32	9.5	31	11
Dysuria	20	6.0	36	12
Renal tubular necrosis	25	7.4	20	6.8
Renal damage	15	4.5	23	7.8
Body as a Whole — General Disorders	124	37	118	40
Pain, posttraumatic	70	21	59	20
Chest pain	29	8.6	26	8.9
Fever	18	5.4	30	10
Pain	24	7.1	24	8.2
Shivering	10	3.0	15	5.1
Autonomic Nervous System Disorders	127	38	105	36
Hypertension	83	25	60	20
Hypotension	29	8.6	30	10
Hypertension, aggravated	25	7.4	21	7.2
Respiratory System Disorders	119	35	107	36
Dyspnea	40	12	45	15
Pulmonary edema	21	6.3	13	4.4
Coughing	17	5.1	14	4.8
Skin and Appendages Disorders	108	32	83	28
Wound healing impaired without infection	41	12	30	10
Acne	30	8.9	21	7.2

Pruritus	13	3.9	17	5.8
Psychiatric Disorders	85	25	86	29
Insomnia	42	12	40	14
Fatigue	25	7.4	28	9.6
Anxiety	7	2.1	16	5.5
Musculoskeletal System Disorders	86	26	77	26
Musculoskeletal pain	42	12	36	12
Back pain	22	6.5	24	8.2
Heart Rate and Rhythm	36	11	35	12
Tachycardia	22	6.5	20	6.8
Vascular (Extracardial) Disorders	39	12	30	10
Thrombosis	18	5.4	13	4.4
Platelet, Bleeding & Clotting Disorders	26	7.7	33	11
Bleeding	25	7.4	31	11
Hemic and Lymphatic Disorders	26	7.7	22	7.5
Lymphocele	25	7.4	19	6.5
Application Site Disorders	18	5.4	15	5.1
Application site reaction	16	4.8	15	5.1

In the combined database consisting of all renal transplant trials, several adverse events were reported somewhat more frequently in the HAT group than in the placebo group including tremor, hypertension and impaired wound healing without infection. Assessment of the individual trials indicates that the frequency of hypertension was higher in the Zenapax (daclizumab)-treated group in both trial NO14874 in which Zenapax (daclizumab) was added to a 2-drug immunosuppressive regimen (21% with Zenapax compared to 15% with placebo) as well as in trial NO14393 in which Zenapax (daclizumab) was added to a 3-drug regimen (30% with Zenapax compared to 27% with placebo). Wound healing impairment without infection was also observed at higher frequency in the Zenapax (daclizumab)-treated groups in both trials: 6.4% with Zenapax compared to 3.0% with placebo in NO14874 and 21% with Zenapax compared to 16% with placebo in trial NO14393.

When adverse event rates were subsetted by gender, the overall incidence of adverse events was similar in the Zenapax (daclizumab) arm and placebo. However, among women there was a higher incidence of nausea, tremor, headache, hypertension and

aggravated hypertension (table 2). Among men, there was a higher incidence of hypertension, impaired wound healing without infection, dizziness, acne, hirsutism and renal artery stenosis (table 2).

Table 2. Adverse events observed at higher frequency in Zenapax group subsetted by gender

	Adverse event rate				
	Zenapax	Placebo		Zenapax	Placebo
Women	98%	95%	**Men**	94%	95%
nausea	40%	35%	**impaired wound healing**	15%	9.0%
tremor	20%	12%	**dizziness**	5.1%	2.6%
headache	23%	18%	**acne**	11%	7.9%
hypertension	24%	21%	**hypertension**	25%	20%
aggravated hypertension	7.5%	4.8%	**hirsutism**	2.3%	0%
			renal artery stenosis	2.3%	0.5%

When adverse event rates were subsetted by age, the overall incidence of one or more adverse events was similar in the Zenapax (daclizumab) arm and placebo (table 3). Among the younger group aged 18-39, there was a higher incidence of: hypertension; nausea; vascular disorders including thrombosis and renal artery stenosis (2 cases vs 0) and one case each of subcutaneous bleeding, hypovolemia, phlebitis, arterial stenosis and a vein disorder; reproductive disorders and disorders in resistance mechanisms including one case each of canker sore, herpes, candida and wound infection. In the group aged 40-60, there was a higher incidence of tremor, headache, pulmonary edema, cough and rales. In the eldest age group (over 60 years of age), there was a higher incidence of tremor, headache, hypertension, insomnia, depression, musculoskeletal pain, wound healing impairment without infection, hirsutism, male reproductive disorders, neoplasms including three skin neoplasms and one lymphoma and disorders of resistance mechanisms consisting of one case each of otitis media and wound infection.

Table 3. Adverse events observed at higher frequency in Zenapax group subsetted by age

	Adverse event rate				
	Zenapax (n=113)	**Placebo (n=83)**		**Zenapax (n=173)**	**Placebo (n=166)**
Age 18-39	96%	94%	**Age 40-60**	94%	94%
hypertension	26%	22%	**tremor**	22%	16%
nausea	31%	23%	**headache**	13%	11%

Vascular disorders	12%	1%	pulmonary edema	6.9%	4.2%
thrombosis	5.3%	0%	cough	6.4%	3.0%
reproductive disorders	6.2%	3.6%	rales	5.2%	1.8%
Resistance mechanism disorders	6.2%	2.4%			

	Adverse event rate				
	Zenapax (n=50)	**Placebo (n=44)**		**Zenapax (n=50)**	**Placebo (n=44)**
Age >60	98%	100%	**Age>60 (cont.)**		
tremor	16%	14%	**impaired wound healing without infection**	18%	9.2%
headache	16%	11%	**hirsutism**	6%	0%
hypertension	34%	16%	**male reproductive disorders**	8.0%	4.5%
insomnia	20%	14%	**neoplasms**	6.0%	0%
depression	8%	2.3%	**Disorders of resistance**	4.0%	0%
musculo-skeletal pain	18%	4.5%			

Overall adverse event rates were similar among non-Caucasians treated with Zenapax (daclizumab) or with placebo (table 4). However, rates of edema of the extremities, pulmonary edema, hirsutism, night sweats, skin ulceration, hypertension, hypotension, muscle cramps and disorders of the hearing and vestibular systems were observed at higher frequency in the Zenapax treated non-Caucasian subjects. The higher frequency of adverse events in the hearing and vestibular system was due to single cases of ear buzzing, earache, fullness in the ears and otitis. The subset of Caucasian subjects had a higher incidence of wound healing impairment without infection, acne, hirsutism and renal artery stenosis.

Table 4. Adverse events observed at higher frequency in Zenapax group subsetted by race

	Adverse event rates				
	Zenapax (n=75)	Placebo (n=67)		Zenapax (n=75)	Placebo (n=67)
Non-Caucasian	98%	100%	**Non-Caucasian**		

			(cont.)		
Edema of extremities	27%	24%	**hypertension**	29%	16%
hirsutism	8.0%	3.0%	**hypotension**	8.0%	4.5%
night sweats	2.7%	0%	**muscle cramps**	4.0%	0%
skin ulceration	2.7%	0%	**Hearing and vestibular disorders**	5.3%	0%

	Adverse event rates	
	Zenapax (n=261)	Placebo (n=226)
Caucasians	98%	100%
Wound healing impairment without infection	12%	9.3%
Acne	8.0%	5.8%
hirsutism	3.8%	1.8%
renal artery stenosis	2.3%	0.9%

Adverse events which were considered remotely, possibly or probably related to study drug were observed with slightly higher frequency in the Zenapax (daclizumab) arm than in the placebo arm (39% compared to 36%). In this category, the adverse events which were observed at higher frequency in the Zenapax (daclizumab) arm included hypertension (6.0% compared to 3.8%), aggravated hypertension (2.7% compared to 1.4%), renal tubular necrosis (5.1% compared to 1.7%) and fever (1.8% compared to 0.3%). In the adverse events categorized as possibly or probably related to study drug, the incidence was slightly higher in the Zenapax (daclizumab) arm compared to the placebo arm (9.5% compared to 7.2%). However, there was no notable increase in any particular type of adverse event. No difference was observed in the proportion of subjects who were prematurely withdrawn from the studies due to adverse events.

Infusion-related adverse events were not observed in the Zenapax (daclizumab)-treated subjects. The incidence of abnormal vital signs immediately after infusion of trial drug and 15 minutes after the infusion ended was similar in the Zenapax (daclizumab) group and the placebo group. No increase was seen in the incidence of abnormal vital signs in patients receiving Zenapax (daclizumab).

As described above, the incidence of hypertension, tremor and wound healing impairment without infection was somewhat higher in Zenapax (daclizumab)-treated subjects than in controls. For tremor and wound healing impairment without infection, these differences in incidence rates were small and were spread fairly randomly across subsets. However, for hypertension, the higher incidence appeared more marked for some subsets. When hypertensive adverse events were subsetted by age, the higher incidence in Zenapax

(daclizumab)-treated subjects was most marked in the greater than 60 year old subset (table 5). When subsetted by ethnicity, the higher frequency of hypertensive adverse events in the Zenapax (daclizumab)-treated groups was most marked in the non-Caucasians (table 6). Finally, when hypertensive adverse events were subsetted based on the etiology of renal failure, the higher frequency observed in the Zenapax (daclizumab)-treated groups was almost entirely accounted for by subjects with hypertensive renal failure and diabetic nephropathy (table 7).

Table 5. Incidence of hypertensive adverse events subsetted by age

	Placebo	Zenapax
Overall	60/293 (20%)	83/336 (25%)
18-39	18/83 (22%)	30/113 (27%)
40-60	35/166 (21%)	36/173 (21%)
≥60	7/44(16%)	17/50 (34%)

Table 6. Incidence of hypertensive adverse events subsetted by ethnicity

	Placebo	Zenapax
Overall	60/293 (20%)	83/336 (25%)
Non-Caucasians	11/67 (16%)	22/75 (29%)
Caucasians	49/226 (22%)	61/261 (23%)

Table 7. Incidence of hypertensive adverse events subsetted by etiology of renal failure

	Placebo	Zenapax
Overall	60/293 (20%)	83/336 (25%)
Diabetes	7/43 (16%)	14/55 (26%)
Hypertension	3/30 (10%)	10/37 (27%)
Other	43/194 (22%)	51/223 (23%)

Data regarding the safety of Zenapax (daclizumab) is also available from patients with steroid–resistant acute graft–versus–host disease in two phase I protocols (N3681 and NO14790). The safety and efficacy of HAT in the prevention of acute graft–versus–host disease in recipients of bone marrow transplants from unrelated donors was studied in one phase II/III protocol (NO14348). Zenapax (daclizumab) was not effective in this indication. The overall incidence of adverse effects was similar in Zenapax (daclizumab)- and placebo-treated groups. The adverse events which were higher in incidence in the Zenapax (daclizumab)-treated group are listed in Table 8. Depression, insomnia and

tremor are adverse events which were observed at higher frequency in Zenapax (daclizumab)-treated groups in the graft-versus-host studies as well as in one or more subsets of subjects in the renal transplant rejection trials.

Table 8. Adverse events observed at higher frequency in Zenapax group in trials studying patients with graft versus host disease

	Adverse event rates				
	Zenapax (n=176)	Placebo (n=65)		Zenapax (n=176)	Placebo (n=65)
Graft-vs-host disease	96%	100%	**general weakness**	15%	4.6%
Abdominal pain	22%	17%	**depression**	20%	12%
Stomatitis	8.5%	4.6%	**insomnia**	11%	7.7%
buccal mucosal ulceration	12%	7.7%	**agitation**	7.4%	3.1%
pyrosis	10%	6.2%	**chest pain**	15%	9.2%
liver and biliary	26%	18%	**edema**	24%	20%
jaundice					
acute renal failure	6.8%	3.1%	**tremor**	25%	15%
renal insufficiency	10%	3.1%			

Zenapax (daclizumab) was assessed in six patients with Tac–bearing tumors. These six subjects are the only ones in the safety database who were not receiving concurrent cyclosporin A or other immunosuppressive agents. The subjects were treated with a single dose of 0.5 mg/kg (4 patients) or 1.0 mg/kg (2 patients) of HAT administered as a 2–hour intravenous infusion, and the patients were then followed for 56 days. The only HAT–related adverse events reported were mild urticaria and flank pain, and moderate leg pain and leg edema in one patient. One serious adverse event (respiratory distress) and one death (from progressive disease) were reported in a single patient during the 56–day follow–up period, and neither was considered related to HAT treatment.

Severe adverse events and deaths

A total of 18 deaths were observed during follow-up of the 4 studies of Zenapax (daclizumab) in renal transplant rejection (table 9). There was 12 mo follow-up in the two phase 3 studies, 6 mo follow-up in the phase 1 study NO15301 and 3 mo follow-up in the phase 1 study NO14392. Fewer deaths occurred among the Zenapax (daclizumab) treated patients than among those treated with placebo. Five deaths (1.5% of those treated) were

in the Zenapax (daclizumab) arm and 13 deaths (4.4% of those treated) were in placebo treated patients. Deaths in the Zenapax (daclizumab)-treated subjects were from suicide (2 cases), intracerebral hemorrhage, lymphoproliferative lymphoma and infective endocarditis.

Table 9. Deaths in renal transplant trials

Cause of death	Zenapax (daclizumab) (n=336)		Placebo (n=293)	
	No. patients	%	No. patients	%
Pneumonia	-	-	2	0.7%
Septic shock	-	-	2	0.7%
Suicide	2	0.6%	1	0.3%
Aspergillosis	-	-	1	0.3
Coccidiodomycosis	-	-	1	0.3
Hemorrhage	-	-	1	0.3
Intracerebral hemorrhage	1	0.3	-	-
Multiple-organ failure	-	-	1	0.3
Pulmonary embolism	-	-	1	0.3
Myocardial infarction	-	-	1	0.3
Collapse, no autopsy	-	-	1	0.3
Coronary artery disease	-	-	1	0.3
Lymphoproliferative lymphoma	1	0.3	-	-
Infective endocarditis	1	0.3	-	-
Total	**5**	**1.5**	**13**	**4.4**

Overall, the incidence of serious adverse events was slightly lower in Zenapax-treated subjects compared to controls (40% compared to 44% with placebo). The most common categories of serious adverse events were urinary disturbances (13% vs 12% with placebo) and infections (9.2% compared to 12% with placebo). Specific serious adverse events observed at higher frequency in the Zenapax (daclizumab)-treated groups included renal insufficiency, renal damage, urinary tract disorder and thrombosis (table 10). Based on examination of the Case Report Forms, many of the cases of renal damage/insufficiency were subjects who developed an elevated creatinine who were biopsied and were found to be negative for rejection. Many of these cases were attributed to cyclosporin A toxicity. The incidence of serious adverse events which were considered by the investigator as attributable in any degree to the study agent was less in the Zenapax (daclizumab)-treated group compared to placebo (14% compared to 20% on placebo). No individual category of attributable serious adverse event was clearly observed at higher frequency in Zenapax (daclizumab)-treated subjects compared to controls.

Table 10. Serious adverse events higher in frequency in the Zenapax (daclizumab)-treated groups in the renal transplant trials

Serious adverse event	Zenapax (daclizumab) (n=336)		Placebo (n=293)	
	No. patients	%	No. patients	%
All SAE	134	40	130	44
Renal damage/insufficiency	20	6%	9	3.0%
Thrombosis	11	3.3%	5	1.7%

Infectious complications

The majority of subjects in the studies of renal transplant rejection experienced one or more infectious episodes. However, the incidence of infection was not elevated in the Zenapax (daclizumab)-treated group (68% compared to 72% with placebo). The most common overall categories of infection were local infections (51% of the Zenapax (daclizumab)-treated and 53% of placebo-treated subjects) and viral infections (25% of the Zenapax (daclizumab)-treated and 28% of placebo-treated subjects) which occurred with a similar incidence in both groups. Most of the specific types of infection were similar in the two groups including CMV infections which were seen in 13% of Zenapax (daclizumab) and 16% of placebo-treated subjects. The one exception was wound infections and cellulitis which occurred in 8.4% of Zenapax (daclizumab)-treated subjects and 4.1% of controls. This difference was statistically significant (nominal p value, $p=0.05$).

Deaths from infections were less frequent in Zenapax (daclizumab)-treated subjects (one case) than in the subjects who received placebo (7 cases) in the four studies of renal transplant rejection.

In the trials which added Zenapax (daclizumab) to 2-drug or to 3-drug immunosuppressive regimens, there was no increase in infectious episodes compared to placebo-treated groups. With the exception of cellulitis and wound infections, there was also no increase in the frequency of any individual type of infection when Zenapax (daclizumab) was added to 2-drug (trial NO14874) or to 3-drug regimens (trial NO14393). However, cellulitis and wound infections were seen in 6% of Zenapax (daclizumab)-treated subjects compared to 3% of controls when Zenapax (daclizumab) was added to a 3-drug regimen. Cellulitis and wound infections was seen in 12% of Zenapax (daclizumab)-treated subjects compared to 5% of controls when Zenapax (daclizumab) was added to a 2-drug regimen. In both studies, deaths due to infection were fewer in the Zenapax (daclizumab)-treated arm than in the placebo arm. In

NO14874, there were no deaths due to infection in the Zenapax (daclizumab)-treated arm and four deaths due to infection in the placebo arm: two from septic shock and two from pneumonia. In NO14393, there were also no deaths due to infection in the Zenapax (daclizumab)-treated group and two deaths from infection in the placebo arm: one from aspergillosis and one from coccidioidomycosis.

In studies of Zenapax (daclizumab) in graft-versus-host disease, the incidence of infectious episodes in recipients of Zenapax (daclizumab) was not observed at higher frequency compared to control. No increase in any particular type of infection was seen and there was no increase in deaths due to infection.

Lymphoid and non-lymphoid malignancies

Data concerning the development of malignancies are available for a one year period of observation in the two phase 3 trials and in one of the two phase 1 trials (NO14392). For the other phase 1 trial, data are available for 6 months of observation. The addition of Zenapax (daclizumab) was not associated with any increase in malignancies when added to a 2- or 3-drug regimen of immunosuppression as 1.5% of Zenapax (daclizumab)-treated and 2.7% of placebo-treated subjects developed malignancies. Four non-melanoma skin tumors and two lymphomas were diagnosed in the Zenapax (daclizumab)-treated group. An equal number of lymphomas were diagnosed in the placebo-treated group. One Zenapax (daclizumab)-treated subject died from lymphoma. This patient was withdrawn from the study after receiving one dose of Zenapax (dacliximab) and developed cerebral lymphoma 7 months after transplantation.

Laboratory abnormalities

The most common laboratory abnormalities seen in the renal transplant studies were low serum phosphorus, elevated ALT, elevated BUN, phosphate and glucose levels, and low calcium and total protein levels. These abnormalities occurred at a similar or lower frequency in the Zenapax (daclizumab)-treated subjects than in placebo-treated subjects with the exception of high fasting blood sugar which was measured in 32% of Zenapax (daclizumab)-treated and 16% of placebo-treated patients. Fasting blood sugar measurements were carried out in less than a third of subjects. Increases in random blood glucose were observed in similar proportions of Zenapax (daclizumab)- and placebo-treated subjects (26% compared to 27% of placebo group). In the graft-versus-host disease trials, the proportion of subjects with elevated fasting blood glucose levels was not elevated.

Co-administration with mycophenolate mofetil

Safety data are available on co-administration of Zenapax (daclizumab) with mycophenolate mofetil from a double-blind randomized trial of Zenapax (daclizumab) added to a three drug immunosuppressive regimen of cyclosporin A, prednisone and

mycophenolate mofetil. Subjects in the Zenapax (daclizumab) arm received 1.0 mg/kg qow for a total of five doses. Seventy-five subjects received at least one dose of study medication including 25 who received placebo and 50 who received Zenapax (daclizumab). Adverse event data were collected for clinical adverse events during the first three months post-transplantation and during the first six months for infectious episodes and lymphoproliferative disorders. There was no difference in the overall rate of adverse events. A higher frequencies of adverse events was seen in the Zenapax (daclizumab)-treated group with regard to hypertension (22% compared to 12% in placebo-treated subjects). A malignancy developed in the Zenapax (daclizumab)-treated group which was a non-melanoma skin tumor. There was no increase in the incidence of adverse events considered to be related to study agent in the Zenapax (daclizumab) group or in the incidence of serious adverse events or infectious episodes. One death occurred in a Zenapax (daclizumab)-treated patient which was assessed to be a suicide.

Studies in children

Study N014348 enrolled approximately equal numbers of subjects under the age of 20 years in a study of : 13 to placebo; 26 to Zenapax (daclizumab) 0.3 mg/kg or 1.2 mg/kg. Of these children, there was one death in the placebo arm, 2 in the 0.3 mg/kg arm and 1 in the 1.2 mg/kg arm. Serious adverse events were observed in seven of these subjects in the placebo arm, nine in the 0.3 mg/kg arm and eight in the 1.2 mg/kg arm.

Anti-Zenapax (daclizumab) antibodies

Anti-idiotypic antibodies to Zenapax (daclizumab) developed in 12% and 18% of subjects who received the study agent in the phase 3 trials of renal transplant rejection NO14393 and NO17874 respectively. No subject who received placebo developed anti-idiotypic antibodies. Rejection occurred in 20% of Zenapax (daclizumab)-treated subjects who developed antibodies and in 18% of those who did not develop antibodies. Pharmacokinetic studies showed that mean and median levels of Zenapax (daclizumab) were not different in antibody-positive and antibody-negative subjects. In the two subjects studied, FACS staining indicated that IL-2 receptors remained saturated throughout therapy despite the presence of circulating antibodies to Zenapax (daclizumab). There is no evidence to suggest that the development of anti-idiotypic antibodies was associated with an increased risk of rejection.

Summary of safety

In a database consisting of 630 subjects treated to prevent renal allograft rejection, there was no observed increase in the overall incidence of adverse events, attributable adverse events, infectious episodes, malignancies or lymphoproliferative disorders. A somewhat higher incidence of hypertension, tremor, impaired wound healing without infection and

renal damage/insufficiency associated with Zenapax was observed in the combined safety database as well as in each of the individual phase 3 studies considered separately. Deaths due to infection and overall mortality were lower in Zenapax (daclizumab)-treated patients compared to placebo-treated patients.

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